Remarks

Claims 56-110 are pending in the subject application. Applicants acknowledge that claims 59, 60, and 86-110 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have amended claims 56-85, 90-92, and 95-104, 107, and 108, and added new claims 111-114. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 59-114 are currently before the Examiner with claims 86-110 standing withdrawn from consideration. Favorable consideration of the pending claims is respectfully requested.

The Examiner notes that the listing of references in the specification is not a proper form for an Information Disclosure Statement (IDS). Applicants submitted an Information Disclosure Statement in the subject application on February 2, 2005 and the Examiner has acknowledged consideration of the IDS in the instant Action. Applicants acknowledge that only those references submitted in their IDS filed February 2, 2005 or cited on form PTO-892 have been considered by the Examiner.

The drawings are objected to under 37 CFR 1.83(a) because they fail to show details as described in the specification. Specifically, Figures 9, 12 and 16 are not legible. Applicants have submitted substitute figures for Figures 9, 12, and 16 with this Amendment. Entry and review of the formal drawings is respectfully requested.

Claim 66 is objected to because of informalities. Applicants gratefully acknowledge the Examiner's careful review of the claims. In accordance with the Examiner's suggestion, Applicants have replaced the phrase "an other" with the word "another" in claim 66. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 56 and 61-85 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action indicates that the specification does not describe IL-7 conformers, other than human conformers, with disulfide bridges at positions Cys:1-4, 2-5 and 3-6. Applicants respectfully assert that there is adequate written description in the subject specification to

convey to the ordinarily skilled artisan that they had possession of the claimed invention and traverse the rejection.

Applicants note that the Office Action argues that only human forms of IL-7 have the recited disulfide bridges [Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47- Cys141)], citing to Kroemer *et al.* in support of this position (Protein Engineering, 1996, 9(6):493-498). As depicted in Figure 5 of the as-filed application, an alignment of human and simian IL-7 indicates that cysteine residues are found at the positions corresponding to positions 2 and 92, positions 34 and 129 and positions 47 and 141 in both the simian and human polypeptide sequence. Thus, Applicants respectfully submit that both simian and human IL-7 sequences possess cysteine residues at the positions recited within the claims and the as-filed specification provides adequate written description of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 71, 80, and 85 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action has rejected the claims for the recitation of "such as" and "comprises". By way of this amendment, Applicants have removed these terms from the claims and respectfully assert that the amended claims are definite. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 56-58, 61, 66, 67, and 81-84 are rejected under 35 U.S.C. § 102(b) as anticipated by Cosenza *et al.* (2000). The Office Action states that Cosenza *et al.* teach a 3-D structure for a recombinant human IL-7 comprising Cys:1-4, 2-5 and 3-6. The Office Action further states that Cosenza *et al.* teach that IL-7 is expressed from *E. coli*, and refolded and purified. In addition, it is indicated that Cosenza *et al.* teach that IL-7 can stimulate pre-B-cell and mature T-cell proliferation, can induce LAK cells and cytolytic T-cells, and may have therapeutic applications in cancer immune therapy and treatment of immune deficiency disease. Applicants respectfully assert that the Cosenza *et al.* reference does not anticipate the claimed invention, particularly, the cited reference fails to teach a drug substance, composition or a composition of matter comprising a human IL-7 or simian IL-7 conformer, wherein said conformer comprises the following three disulfide bridges: Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47- Cys141), the total amount by weight of IL-7 in said drug substance, composition or a composition of matter is at least 98% by weight and wherein

said drug substance, composition or a composition of matter is substantially free of IL-7 molecular variants or product related impurities.

Applicants submit that the cited reference fails to teach the claimed IL-7 conformers. Contrary to the assertion in the Office Action, Cosenza *et al.* teach that the hIL-7 molecule contains cysteine residues at positions (according to the numbering used in this application) Cys: 1-6 (Cys2- Cys141); 2-5 (Cys34- Cys129) and 3-4 (Cys47- Cys92). This is clearly set forth in the upper panel of Figure 3B within the reference (referring to the Cosenza *et al.* model). This assignment of disulfide bonds is, once again, reiterated at page 918, column 1, *Construction of an IL-7 structural hypothesis*, last sentence where it is stated "The three disulfide bond assignments are composed of cysteine residue pairs (Cys3, Cys142), (Cys35, Cys130) and (Cys48, Cys93)". These cysteine residues correspond to Cys: 1-6 (Cys2- Cys141); 2-5 (Cys34- Cys129) and 3-4 (Cys47- Cys92) as numbered in this application. Thus, it is clear that Cosenza *et al.* do not teach a human or simian IL-7 conformer containing the following disulfide bridges: Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47- Cys141). It is also noted that the Office Action argues that the 3-D model was constructed for a pure molecule (*e.g.*, IL-7 in a crystal); however it is submitted that a computer generated model is not a drug substance, composition or a composition of matter, rather it is a theoretical representation of a molecule presented in a written form. Furthermore, the model generated by Cosenza *et al.* does not teach the claimed IL-7 conformer. Rather, it teaches a conformer comprising a different set of disulfide bridges (see page 918, column 1, *Construction of an IL-7 structural hypothesis*, last sentence). Thus, it cannot be reasonably asserted that the crystal structure discussed in the Office Action anticipates the claimed invention, particularly in view of the express teachings of the reference with respect to the formed disulfide bonds. Accordingly, the cited reference fails to anticipate the claimed invention and reconsideration and withdrawal of the rejection is respectfully requested.

With respect to a theoretical representation of a molecule only in a written form, the mere written description of a biological material does not normally enable a person skilled in the art to reproduce a specific, claimed biological material. *In re LeGrice*, 301 F.2d 929, 133 U.S.P.Q. 365 (1962)(holding that a mere written description of a "rose floribunda plant" would not normally enable a person skilled in the art to reproduce the plant, since plant breeders "are not presently able

to control the factors which govern the combination of genes and chromosomes required to produce a new plant having certain predetermined desired properties"; that "[s]hould a plant variety become extinct one cannot deliberately produce a duplicate even though its ancestry and the techniques of cross-pollination be known"; and that the prior publication did not meet the legal requirements for the bar stated in 35 U.S.C.A. § 102(b) as it did not communicate where the necessary starting material could be obtained).

Applicants further submit that the holding in *LeGrice* is not limited to plant materials. *Ex parte Argoudelis* (157 U.S.P.Q. 437, 440 (Pat. & Trademark Office Bd. App. 1967), rev'd on other grounds, 58 C.C.P.A. 769, 434 F.2d 1390 (1970)) applied the LeGrice holding to claims directed to an isolated antibiotic and methods of making an antibiotic produced by a strain of microorganism and a reference asserted to anticipate the claimed invention. As stated by the Board of Appeals in that decision (regarding the publication cited as prior art), "It cannot be denied that *In re LeGrice* applies to the publication cited in this application to the same extent that it applied to the publications cited in that case. Moreover, we have ourselves held that a written description of the character involved in a case such as the present one is not sufficient to enable a person skilled in the art to produce the invention." Finally, it is also respectfully submitted that the Court of Appeals for the Federal Circuit has also held that the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (holding that "[w]ithout a disclosure enabling one skilled in the art to produce a transgenic mouse without undue experimentation, the reference would not be applicable as prior art). Similarly, chemical compounds that are described in a written form are also not considered to be anticipatory in the absence of an enabling disclosure. See *In re Wiggins,* 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1971)(when a prior art reference merely discloses the structure of the claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of invention will be adequate to show inoperability). In this case, Applicants respectfully submit that attempts to make the claimed compound (human or simian IL-7 conformers having the recited disulfide bonds) were unsuccessful as evidenced by the teachings in the prior art that assigned

disulfide bonds at (Cys3, Cys142), (Cys35, Cys130) and (Cys48, Cys93) (corresponding to cysteine residues Cys: 1-6 (Cys2- Cys141); 2-5 (Cys34- Cys129) and 3-4 (Cys47- Cys92) as numbered in this application). Accordingly, it is respectfully submitted that the cited reference fails to anticipate the claimed reference and reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claims 62, 68-80, and 85 are rejected under 35 U.S.C. § 103(a) as obvious over Cosenza *et al.* (2000) in view of Namen *et al.* (U.S. Patent No. 4,965,195), and further in view of Ho *et al.* (U.S. Patent No. 5,714,141). The Office Action indicates that it is obvious to one of ordinary skill in the art to combine the teachings of Cosenza *et al.*, with those of Namen *et al.* and Ho *et al*, to prepare an IL-7 conformer from a mammalian expression system and use the protein to make pharmaceutical compositions. Applicants respectfully assert that the claimed invention is not obvious over the cited references. As noted above, the IL-7 conformer taught to exist by Cosenza *et al.* contains disulfide bonds at cysteine residue pairs (Cys3, Cys142), (Cys35, Cys130) and (Cys48, Cys93) (page 918, column 1, *Construction of an IL-7 structural hypothesis*, last sentence). These residue pairs correspond to Cys: 1-6 (Cys2- Cys141); 2-5 (Cys34- Cys129) and 3-4 (Cys47- Cys92) as numbered in this application. Thus, it is clear that Cosenza *et al.* do not teach a human or simian IL-7 conformer containing the following disulfide bridges: Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47- Cys141). Namen *et al.* and Ho *et al.* fail to remedy this defect in Cosenza *et al.* and it is, thus, respectfully submitted that the cited combination of references fails to render the claimed invention *prima facie* obvious. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 63-65 are rejected under 35 U.S.C. § 103(a) as obvious over Cosenza *et al.* (2000) in view of Goldschneiser *et al.* (U.S. Publication No. 2002/0058791 A1) and further in view of Goeddel *et al.* (U.S. Patent No. 5,223,408). The Office Action asserts that Goldschneiser *et al.* teach a hybrid cytokine of IL-7 and HGF β-chain as a pre-pro-B cell growth stimulating factor that exhibit unique lymphopoietic properties and that the IL-7/HGFβ can be joined by disulfide-bridges produced by the two polypeptides. The Office Action further asserts that Goeddel *et al.* teach conjugating an immunogenic polypeptide with Ig Fc or albumin to increase half-life. Applicants respectfully assert that the claimed invention is not obvious over this combination of cited references.

As previously argued, the IL-7 conformer taught to exist by Cosenza *et al.* contains disulfide bonds at cysteine residue pairs (Cys3, Cys142), (Cys35, Cys130) and (Cys48, Cys93) (see page 918, column 1, *Construction of an IL-7 structural hypothesis*, last sentence). These residue pairs correspond to Cys: 1-6 (Cys2- Cys141); 2-5 (Cys34- Cys129) and 3-4 (Cys47- Cys92) as numbered in this application. Thus, it is clear that Cosenza *et al.* do not teach a human or simian IL-7 conformer containing the following disulfide bridges: Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47- Cys141). Goldschneiser *et al.* and Goeddel *et al.* fail to remedy this defect in Cosenza *et al.* and it is respectfully submitted that the cited combination of references fails to render the claimed invention *prima facie* obvious. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Applicants further submit that the claimed IL-7 conformers possess unexpectedly different properties as compared to other forms of IL-7. As is indicated in the specification, purified IL-7 compositions comprising the claimed IL-7 conformers (containing the disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129); and 3-6 (Cys47-Cys141)) demonstrate biological activities that differ from other IL-7 compositions (see Examples H, I, and J; pages 59-64). These differing biological activities include reduced immunogenicity of the claimed drug substance, composition or composition of matter, increased CD4 T-cell counts in animals treated with the claimed drug substance, composition or composition of matter, and irradiated animals treated with the claimed drug substance, composition or composition of matter exhibited increased CD4 cell counts for a longer period of time as compared to irradiated animals treated with other forms of IL-7 (Figure 13). Accordingly, it is respectfully submitted that drug substances, compositions or compositions of matter containing the claimed IL-7 conformers have unexpectedly different properties as compared to other forms of IL-7 and that these properties are evidence related to the non-obviousness of the claimed invention.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including

any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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Attachments: Replacement Figures 9, 12, and 16